

## **REMARKS**

Claims 24, 27, 28, and 33-49 are pending in the present application. Claim 24 has been amended to include the elements previously recited in claims 25 and 26, which have been cancelled. Claims 29-32 have also been cancelled. Claim 33 has been amended to incorporate the elements of cancelled claim 32, from which claim 33 previously depended. Claims 34-49 have been withdrawn from consideration.

The amendments to the claims are supported by the application as originally filed, do not add new matter, and are otherwise proper. Applicants respectfully request entry of this Amendment in its entirety. The foregoing claim amendments and cancellations are made without prejudice solely to advance the prosecution of this application. In view of the above amendment and following remarks, applicants respectfully request reconsideration of the claims and submit that the application is in condition for allowance. This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, are presented, with an appropriate defined status identifier.

### **I. Oath Declaration**

The Office Action noted that the oath or declaration was defective. Applicants are in the process of having a new oath or declaration prepared and would like to thank the Examiner for the telephone communication of July 29, 2003, confirming that the new oath or declaration and is not required to accompany the present Amendment and Reply. Accordingly, applicants respectfully request that this objection be held in abeyance until applicants are able provide the new oath or declaration.

### **II. Specification**

In the Office Action, the specification was objected to because "the preliminary amendment filed June 20, 2001, amends the specification to indicate related applications, however, the specification as filed contains the same information in the first line of the specification. One of the two recitations of the priority information should be deleted."

Applicants have reviewed the papers filed in the present application and the Examiner is correct that the preliminary amendment filed June 20, 2001, amended the first paragraph of the specification to indicate related applications. However, the original application filed on June 20, 2001, did not contain this reference to related applications. Applicants note that the Substitute Specification filed December 26, 2001, did contain the reference to related applications based on the preliminary amendment filed June 20, 2001. Accordingly applicants do not believe that the present application contains two references to related applications or that an amendment in this regard is necessary. However, should the present application contain multiple references to related applications, applicants respectfully request that one of the references be deleted.

### **III. Claim Rejections – 35 U.S.C. §112**

In the Office Action, claim 33 was rejected under 35 U.S.C. 112, first paragraph as non-enabled. The Examiner indicated that “the requirements of 35 U.S.C. 112, regarding ‘how to make’, may be satisfied by a deposit of the dMsh2-9 cell line.” Applicants are in the process of depositing the dMsh2-9 cell line in accordance with the terms of the Budapest Treaty and will provide the required affidavit or statement once deposit of the cell line has been confirmed. Accordingly, applicants respectfully request that this rejection be held in abeyance until applicants provide the required affidavit or statement.

### **IV. Claim Rejections – 35 U.S.C. §102**

In the Office Action, claims 24, 26, and 27 were “rejected under 35 U.S.C. 102(b) as being anticipated by Reenan *et al.* (Genetics 132:975-985)” because “Reenan *et al.* teach that yeast have a homolog of mammalian Msh2.” Applicants respectfully traverse this rejection because claim 24, as amended, specifies that the cell is a mammalian cell. Reenan *et al.* cannot anticipate claims 24, 26 and 27 because Reenan *et al.* deal solely with yeast cells. Accordingly, applicants respectfully request the Examiner withdraw this rejection.

Claims 29, 30 and 32 were “rejected under 35 U.S.C. 102(b) as being anticipated by Umar *et al.* (JBC 269:14367-14370)” and also “under 35 U.S.C. 102(a) as being anticipated by Orth *et al.* (PNAS 91:9495-9499). Claims 29, 30 and 32 have been cancelled obviating the

grounds for these rejections. Accordingly, applicants respectfully request the Examiner withdraw these rejections.

**V. Claim Rejections – 35 U.S.C. §103**

In the Office Action, claims 24-30 and 32 were rejected as obvious over Varlet *et al.*, Genbank accession number x81143 and Berns *et al.* (U.S. Patent No. 5,789,215 or WO 93/04169) because “Varlet *et al.* teach that further in vivo analysis of the role of Msh2 is required and that the study of genetics in mice will provide further insight on the development of cancer, therefore it would have been *prima facie* obvious... to take the specific Msh2 sequences disclosed and suggestion by Varlet *et al.* to make mouse embryonic stem cells with a disrupted Msh2 using the knock-out methodology described by Berns *et al.*” Applicants respectfully traverse this rejection. Applicants first note that claims 25, 26, 29, 30 and 32 have been cancelled and, therefore, respectfully request the Examiner withdraw this rejection with respect to these claims.

In order to “establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art.” MPEP §2143.03. Based on this standard, the combination of Varlet *et al.* and Berns *et al.* cannot render the rejected claims *prima facie* obvious because this combination of references fails to teach or suggest all the elements of the rejected claims. Specifically, neither Varlet *et al.* nor Berns *et al.* teach or suggest inactivating the mismatch repair system of a mammalian cell by disrupting both copies of a gene essential for mismatch repair. In fact, neither reference teaches or suggests that the mismatch repair system of a mammalian cell can be inactivated as claimed in the present invention. Varlet *et al.* teach at most that there is some correlation between the mammalian Msh2 gene and the replication correction process. Nowhere do Varlet *et al.* suggest that the Msh system can be inactivated by disrupting both copies of the Msh gene. Berns *et al.* cannot overcome this deficiency because they merely disclose a tool for disrupting a gene of interest but never mention the mismatch repair system of mammalian cells.

At best, the cited references suggest that it would be obvious to try and make the claimed invention. However, the “obvious to try” test is not the standard by which patentability

of an invention is judged. MPEP §2145 X.B. Although the Office Action states that “Varlet *et al.* indicate the types of further research required to address their hypothesis” and there is a “suggestion by Varlet *et al.* to make mouse embryonic stem cells with a disrupted Msh2” the Office Action fails to recite the portion of Varlet *et al.* that supports either of these statements. Applicants respectfully disagree that Varlet *et al.* make or support these statements and respectfully request the Examiner point out the support in Varlet *et al.* for these statements.

As pointed out by the Examiner, Varlet *et al.*’s statement that “further study of the biochemistry (in *Xenopus* egg lysates) and of the genetics (in mouse) of mismatch repair will shed new light on [Msh2’s] role” simply provides a starting point from which to conduct additional experiments on the Msh2 gene. It appears that this general statement, however, is used as the sole basis for the very specific “suggestion by Varlet *et al.* to make mouse embryonic stem cells with a disrupted Msh2[.]” Applicants respectfully submit Varlet *et al.*’s position has been overstated in the Office Action. In fact, one skilled in the art would recognize that the teachings of Varlet *et al.*, and specifically the statement that “further study... will shed light on its role,” are nothing more than an “invitation” for the skilled to further experiment on the Msh2 gene. “Further study...” is vague enough to encompass virtually any type or amount of experimentation. As such, Varlet *et al.*’s teachings do not provide sufficient guidance or specificity as to what experimentation should be performed or what results might be achieved by such experimentation. The Examiner explicitly recognizes these facts when she states that “however [Varlet *et al.*] do not provide the specific guidance to provide a model system.” Berns *et al.* cannot overcome these fundamental deficiencies of Varlet *et al.* because Berns *et al.* are cited merely for providing a specific experimental tool which has no specific relationship to the mismatch repair system of a mammalian cell. Accordingly, applicants respectfully request the Examiner withdraw this rejection because the invention has been measured against the improper obvious to try standard.

Claims 29-31 were also rejected “under 35 U.S.C. 103(a) as being unpatentable over Varlet *et al.*, Genbank accession number x81143, and Berns *et al.* (US Patent 5,789,215 or

WO 93/04169) in view of Promega Protocols and Applications Guide.” Applicants have cancelled claims 29-31 have been and respectfully request the Examiner withdraw this rejection.

### CONCLUSION

In view of the above remarks and amendments, it is respectfully submitted that this application is in condition for allowance. Early notice to that effect is earnestly solicited. The Examiner is invited to telephone the undersigned at the number listed below if the Examiner believes such would be helpful in advancing the application to issue.

Respectfully submitted,

Date September 3, 2003

By 

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